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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,328	11/20/2003	Nizal Samuel Chandrakumar	3077/0A	1053

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 06/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/718,328	CHANDRAKUMAR ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.G.D

Pursuant to preliminary amendment, claims 1-12 have been cancelled, and claims 13-22 added. Claims 13-22 are pending.

✦

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-22 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown (pages 233-240) some propensity of the claimed compounds to antagonize $\alpha_v\beta_3$ and IIb/IIIa. Accordingly, it is stipulated that the following claim is enabled:

> *A method of inhibiting angiogenesis comprising administering a compound [of formula I] to a mammal in need thereof for a time and under conditions effective to antagonize the $\alpha_v\beta_3$ integrin.*

However, it does not necessarily follow therefrom that the claimed compounds are effective to treat cancer, or any of the other diseases recited in the claims.

The disclosure of Carron (*Cancer Res* 58, 1930-35, 1988) is acknowledged. Carron has shown that the compound designated SC 68448 achieved all three of the following:

(a) inhibited vitronectin binding to the $\alpha_v\beta_3$ receptor; (b) inhibited angiogenesis in rat corneas; and (c) inhibited the growth of tumors in immune-compromised rats. Applicants have argued that since this one compound exhibited these properties, it follows therefrom that any compound which inhibits vitronectin binding to the $\alpha_v\beta_3$ receptor will be effective to reduce tumor volumes in mammals. However, applicants are not correct about this extrapolation. As stated in *Ex parte Forman* (230 USPQ 546, 1986). and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, structure/activity relationships are "unpredictable" in pharmacology generally, but specifically the case of integrin/ligand interactions.

Consider the following:

- Dutta (*Journal of Peptide Science* 6, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both in vitro and in vivo:
  cyclo[Ile-Leu-Asp-Val-NH $(CH_2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)
  These peptides are minor variations of peptides that were active.

- Arrhenius (USP 5,688,913) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of a4ß1 activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* 126(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

- As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, $\alpha_v\beta_3$ is sufficiently related to VLA-4 that a finding of "unpredictability" in structure activity relationships of one of these two integrins suggests the same for the other (of the two).

- Haubner (*J. Am. Chem. Soc.* 118, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the αIIß1 receptor, and vitronectin binding to the $\alpha_v\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity.

As indicated above, it is stipulated that angiogenesis will be inhibited by the claimed compounds. But mere inhibition does not equate with a therapy. For a therapy to be "successful", the patient's condition must improve perceptively. Mere inhibition of angiogenesis and of tumor cell proliferation does not guarantee such success. If the degree of inhibition is insufficient, an improvement in the patient's condition will not be realized. The assertion is that, because structure/activity relationships are unpredictable in the case of ligand/integrin interactions, the degree of $\alpha_v\beta_3$ antagonism by the claimed compounds may well be less than the compound (designated SC 68448) disclosed in Carron (*Cancer Res* 58, 1930-35, 1988). As indicated above, minor changes in structure can lead to complete loss of activity. While complete loss of activity is not being asserted, at least in the case of $\alpha_v\beta_3$ antagonism, some loss of activity may have occurred

in making the transition from SC 68448 to the claimed compounds. In addition to the matter of unpredictability in the case of $\alpha_v\beta_3$ antagonism, there is also the matter of bioavailability/pharmacokinetics, and xenobiotic metabolism. These paramaters will all change (in unpredictable ways) with structure of the compounds. Consider also the following:

- Nicosia (*American Journal of Pathology* 138 (4) 829-33, 1991) discloses that the peptide GRGDS is effective to inhibit angiogenesis, but that if the aspartic acid side chain is extended by just one methylene group, loss of activity results. Thus, the conclusion is that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned.

- Belo (*Inflammation* 25 (2) 91-6, 2001) discloses that thalidomide inhibited angiogenesis in mice, but failed to inhibit tumor growth in the same mouse strain.

- Mundhenke (*Clinical Cancer Research* 7 (11) 3366-74, 2001) disclosed the results of a phase I clinical trial with endostatin, which is an angiogenesis inhibitor. The result is that the endostatin was not particularly effective in treating cancer patients.

Thus, one can conclude from the foregoing three references that not only is it true that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned, but in addition, even if angiogenesis can be achieved by a given compound "X", reduction of tumor volumes by the compound "X" is "unpredictable".

In accordance with the following, "undue experimentation" would be required to treat the various diseases that are recited in the claims.

✧

Claims 13-22 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 13 recites that "HET" is a 5-8 membered heterocyclic ring. However, the structural formula recited in claim 13 doesn't contain "HET" *per se*, but instead contains a group that also includes "X1". Thus, is it the case that when X1 is an atom of nitrogen sulfur or oxygen that the upper limit of heteratoms is 5, or is it the case that "HET" is a 5-8 membered heterocyclic ring which necessarily includes X1...?

- Claim 16 characterizes angiogenesis as a "condition"; similarly claim 19 characterizes smooth muscle migration as a "condition". However, these processes occur in normal healthy humans. As such, mitigating these processes could result in induction of a pathological state, where none existed previously. What is the purpose of inhibiting these processes in normal healthy humans?

- Claim 13 is drawn to a method of "treating" a condition; claim 20 recites that, as a consequence of treating an unnamed condition, the result is inhibition of restenosis. What then is the unnamed condition that is being treated, such that inhibition of restenosis results? One option here would be to cast claim 20 in independent form.

✧

Those references which have been stricken from the IDS were not received, and are not present in the parent application file.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600